REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 7, 9, 13, 15, 19, and 31-39 will be pending in this application and presented for examination. Claims 7, 13 and 19 have been amended. Claims 1-4, 8, 10, 14, 16 and 28-30 have been canceled without prejudice or disclaimer. Claims 31-39 are newly added. No new matter has been introduced with the foregoing amendments and new claims. Reconsideration is respectfully requested.

I. FORMALITIES

Independent claims 7, 13 and 19 have been amended to incorporate the features of claims 8 and 10. These features are that interferon α is natural interferon α and that the vaccine antigen is a peptide or protein.

Claims 31-39 are newly added. Claims 31, 34, and 37 recite the features that the mucosa is the intestinal mucosa as found in Example 2. Claims 32-33, 35-36, and 38-39 recite that the antibody in blood is IgG, whereas the antibody secreted at the mucosal surface is IgA. Support is found at the bottom of page 9, last 3 lines. As such, Applicants respectfully request that these amendments and new claims be entered.

II. REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-4, 7-10, 13-16, and 19 under 35 U.S.C. § 103(a) as allegedly being obvious over WO 00/20028 ("Staats *et al.*") in view of Takasu, *Kurume Med J., 2001,* Vol. 48, p. 171-174 ("Takasu"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Staats *et al.* teach a method for eliciting an immune response against an antigen in a vertebrate by providing an antigen-adjuvant composition. Staats *et al.* teach the use of a substantially non-toxic adjuvant and exemplifies IL-1α and IL-1β. Staats *et al.* teach a method wherein *interferon-gamma* is used. Further, Staats *et al.* do not teach or suggest a systemic immune and a mucosal immune response can be induced by concomitant use of interferon α and an antigen by nasal administration.

Takasu teaches away from the present invention. Takasu teaches that the antigen peptide is administered continuously by *osmotic pump*, while the INF-α is *injected* at the site of peptide inoculation. There is absolutely no teaching or suggestion of a nasal administration as is currently claimed, nor is there any teaching of the adjuvant and the peptide being administered at the same time.

Applicants have amended the independent claims to incorporate the features of claims 8 and 10. Claim 7 is exemplary and sets forth the following:

> 7. A mucosal adjuvant for inducing both vaccine antigen-specific antibody in blood and vaccine antigen-specific antibody secreted at the mucosal surface, comprising a natural interferon α as the active ingredient of said mucosal adjuvant and wherein nasal mucosal administration of said mucosal adjuvant is performed at the same time as a vaccine antigen, wherein said vaccine antigen comprises a protein or peptide antigen.

In this regard, the Examiner's attention is respectfully directed to Example 2, at the bottom of page 13, bridging to page 14 of the English specification. Example 2 is set forth below for the Examiner's convenience.

> Example 2
> As in example 1, OVA was administered at 100 μg/mouse per dose to four or five C57BL mice (males, 8 weeks old) per group. Interferon α was administered at the same time as the antigen at 1.5 μg/mouse. Administration was always nasal administration. After administration a total of three times, the initial administration and one week and two weeks after [the initial administration], an approximately one-day sample of feces was collected beginning the day before the third week, fourth week, and sixth week from the day of the initial administration. Exactly 250 mg of this feces sample were weighed out, 1 ml of Tris hydrochloride buffer (pH of 7.4) was added and stirred, and then this was centrifuged for 15 minutes at 3,000 rpm and the supernatant was recovered. The OVA-specific antibody titer in the supernatant (fecal IgG) was assayed by the ELISA method (Table 2).

Comparative Example 2

OVA was administered at 100 μg/mouse per dose to five C57BL mice (males, 8 weeks old) per group. Administration was always nasal administration. After administration a total of three times, the initial administration and one week and two weeks after [the initial administration], an approximately one-day sample of feces was collected beginning the day before the third week and fourth week from the day of the initial administration. Exactly 250 mg of this feces sample were weighed out, 1 ml of Tris hydrochloride buffer (pH of 7.4) was added and stirred, and then this was centrifuged for 15 minutes at 3,000 rpm and the supernatant was recovered. The OVA-specific antibody titer in the supernatant (fecal IgG) was assayed by the ELISA method (Table 2).

Table 2. OVA-specific fecal IgA titer in Example 2 and Comparative Example 2

	OVA-specific fecal IgA titer (OD 490 nm)	
	Comparative Example 2	Example 2
3 w	0.16 0.51 0.55 0.61 0.76	0.74 0.85 0.86 0.87
4 w	0.46 0.57 0.71 0.76 2.34	0.62 1.09 1.12 1.27

Discussion

As shown in Table 2, Example 2 showed a significantly high OVA-specific fecal IgA titer when compared to Comparative Example 3 [sic 2], particularly during the third and fourth weeks, ***and therefore, an immune response was induced on the gastrointestinal mucous membranes by concomitant use of interferon α by nasal administration. These results indicate that a systemic immune response as well as a mucosal immune response can be induced by concomitant use of interferon α by nasal administration.***

This data clearly illustrates that the claimed mucosal adjuvant induces both vaccine antigen-specific antibody in the blood and vaccine antigen-specific antibody secreted at the mucosal surface (*e.g.*, at the gastrointestinal mucosa). That is, when a mucosal adjuvant comprising a natural interferon α and a vaccine antigen comprising a protein or peptide is administered via the nasal mucosal ***a systemic immune response is induced as well as a mucosal immune response.***

Applicants can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillion*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990). Applicants maintain that a *prima facie* case of obviousness has not been established. However, comparative data filed with the application rebuts any *prima facie* case of obviousness. As the data illustrates, nasal administration of the vaccine antigen and natural INFα induces both a vaccine antigen-specific antibody in the blood and a vaccine antigen-specific antibody secreted at the mucosal surface. This objective evidence rebuts any *prima facie* case of obviousness. As such, Applicants respectfully request that the Examiner withdraw the rejection.

III. REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-19 under 35 U.S.C. § 103(a) as allegedly over U.S. Patent No. 6,436,391 ("Foster *et al.*") in view of U.S. Patent No. 6,361,769 ("Tovey"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Foster *et al.* teach an adjuvant for a vaccine comprising IFN-α_8 and/or IFN-α_{14}. Foster *et al.* do not teach or suggest the administration of natural IFNα with a peptide or protein antigen nasally at the same time. Tovey teaches a method for stimulating the immune response by administering an interferon via oromucosal contact. There is no teaching or suggestion of a mucosal adjuvant comprising a natural interferon α and an antigen comprising a protein or

peptide antigen being administered via the nasal mucosal eliciting ***a systemic immune response as well as a mucosal immune response.***

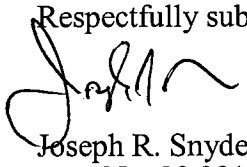
As such, neither Foster *et al.* nor Tovey teach or suggest the administration of IFNα with the vaccine antigen nasally at the same time to elicit ***a systemic immune response as well as a mucosal immune response.*** Nasal administration of a vaccine antigen and an INFα that induces both a vaccine antigen-specific antibody in the blood and a vaccine antigen-specific antibody secreted at the mucosal surface is not taught or suggested in the combination of the cited art.

In the present invention, when a mucosal adjuvant comprising a natural interferon α and a vaccine antigen comprising a protein or peptide is administered via the nasal mucosal ***a systemic immune response is induced as well as a mucosal immune response.*** This objective evidence rebuts any *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
JS:js
61118910 v1